from Gotter, et al. (*Tumor Targeting* 1:107-14, 1995; page 108, left col., Amplification and sequencing of antibody DNA). The article by Dübel, et al. is referenced in the present application on page 2, lines 25 and 29. The article by Gotter, et al. is referenced in the present application on page 2, lines 31-32. Applicants state that the inserted material corresponds to the sequences disclosed by Dübel, et al. and Gotter, et al., as cross-referenced in the present application. A declaration to this effect is enclosed with this Response.

The specification is amended to clarify that the description of Figure 3 includes Figures 3A and 3B.

Claim 1 is amended to recite "the antibody produced by the hybridoma of ATCC deposit number CRL 8001". Support for the amendment is found, for example, at page 1, lines 12-16.

Claim 1 is amended to recite "wherein said recombinant antibody product comprises the amino acid sequence depicted by SEQ ID NO:2". Support for the amendment is found, for example, in Claim 3 as originally filed and at page 5, lines 15-16.

Claims 3, 8, 15-17 and 22 are cancelled in order to expedite prosecution.

Claim 4 is amended to recite "according to claim 1 or 2". Support for the amendment is found, for example, in Claim 4 as originally filed.

Claim 4 is amended to recite "ATCC deposit number CRL 8001". Support for the amendment is found, for example, at page 1, lines 12-16.

Claim 5 is amended to recite "the amplifying of step b) uses primers having the nucleotide sequences depicted by SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10 and SEQ ID NO:11". Support for the amendment is found, for example, in the amended paragraph of page 2.

The above amendments are made solely in order to expedite prosecution of the application. Applicants reserve the right to file the original claims in one or more continuation-type application.

No new matter is added in any of the above amendment and the Examiner is respectfully requested to enter the amendments and reconsider the application.

The Response

1. Objection to Formal Drawings

Applicants submit with this Response two sheets of corrected formal drawings of Figures 3A and 3B. Applicants respectfully contend that said corrected formal drawings are fully compliant with 37 C.F.R. §1.84, and have corrected the informalities objected to by the Reviewer in the Notice of Draftperson's Patent Drawing Review dated May 2, 2001.

2. Objection to specification

The Examiner objects to the specification for failure to comply with the requirements of 37 CFR §1.77. Applicants amend specification by inserting the Section Headings as described at 37 CFR §1.77(c). In light of these amendments, Applicants contend that the specification is fully compliant with the requirements of 37 CFR §1.77, and respectfully request the Examiner to withdraw this objection.

3. Objection under 37 CFR 1.821(d)

The Examiner objects to Claim 5 for failing to recite the SEQ ID NOs. Applicants have amended Claim 5 to recite the appropriate SEQ ID NOs. Amended Claim 5 identifies the primers by the nucleotide sequences as depicted by SEQ ID NO:8-11. Therefore, in view of the amendment, the Examiner's objection should be withdrawn.

4. 35 U.S.C. § 112, second paragraph rejections.

In the Office Action dated May 7, 2001, the Examiner rejected Claims 1-9 in that allegedly the term "OKT3" is a trademark or trade name. Applicants respectfully avoid this basis of rejection by amending the Claims 1 and 4 to recite "the antibody produced by the hybridoma of ATCC deposit number CRL 8001" as suggested by the Examiner. Claims 3 and 8 are cancelled. Claim 2 depends from Claim 1, and Claims 5-7 and 9 depend from Claim 4. Therefore Claims 1, 2, 4-7 and 9, as amended, are clear and definite. The Examiner is respectfully requested to withdraw this rejection.

The Examiner rejects Claims 2, 5, 8, 12, 13, 15-17, 19 and 22 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The rejection of Claims 2, 5, 12, 13 and 19 is overcome in view of the amendments. Claims 8, 15-17 and 22 are cancelled.

A) The Examiner rejects Claim 2 in that allegedly there is insufficient antecedent basis for "The recombinant antibody product" and "the polar amino acid". Claim 2 is amended to depend from Claim 1. Amended Claim 2 has antecedent basis for "The recombinant antibody product" and "the polar amino acid" in Claim 1. Therefore amended Claim 2 is clear and definite.

B) The Examiner rejects Claims 5, 12, 13 and 19 in that allegedly there is insufficient antecedent basis for "the primers". Claim 5 is amended to recite "the amplifying of step b) uses primers having the nucleotide sequences depicted by SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10 and SEQ ID NO:11". Amended Claim 5 does not recite "the primers" and thus does not require an antecedent basis for the term "primers". Therefore amended Claim 5, and Claims 12, 13 and 19 that depend from Claim 5, are clear and definite.

C) The Examiner rejects Claims 8, 15-17 and 22 in that allegedly the term "pHOG21" is indefinite because its characteristics are not known. Claims 8, 15-17 and 22 are cancelled.

For the reasons above, the § 112, second paragraph rejection of Claims 2, 5, 8, 12, 13, 15-17, 19 and 22 should be withdrawn.

5. 35 U.S.C. § 112, first paragraph, enablement rejection.

The Examiner rejects Claims 8, 15-17 and 22 under 35 U.S.C. § 112, first paragraph because allegedly "the pHOG21 vector is required to practice the claimed invention". Claims 8, 15-17 and 22 are cancelled. Therefore, this 35 U.S.C. § 112, first paragraph rejection should be withdrawn.

6. 35 U.S.C. § 102(a)

The Examiner rejects Claims 1-9, 12-25 and 27 under 35 U.S.C. § 102(a) as being anticipated by Kipriyanov, et al. (*Protein Engineering* 10(4):445-53, 1997). The Applicants respectfully traverse this rejection because (1) Kipriyanov, et al. (1997) is not a prior art reference under 35 U.S.C. § 102(a), and (2) Kipriyanov, et al. (1997) does not disclose a recombinant antibody product or peptide comprising the amino acid sequence depicted by SEQ ID NO:2.

The legal standard for a novelty rejection is that a claim is anticipated only if each and every element as forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

Kipriyanov, et al. (1997) is not a prior art reference under 35 U.S.C. § 102(a). An English translation of the priority document, German Patent Application No. 187 21 700.1, and a statement that the English translation is accurate, pursuant to 37 CFR §1.55(a)(4) are enclosed. Therefore the present application claims priority to the filing date of the '700.1 application, which has a filing date of May 23, 1997, and has a priority date earlier than the publication date of Kipriyanov, et al. (1997). In the Response to Office Action, dated October 9, 2001, we provided a correspondence from the Production Editor of the Oxford University Press indicating that the *Protein Engineering* Volume 10, No. 4, 1997 issue was dispatched on June 2, 1997.

In addition, Claims 1-9 and 12-22 contain the element of a recombinant antibody product comprising the amino acid sequence depicted by SEQ ID NO:2. Claims 23-25 and 27 contain the element of a peptide comprising the amino acid sequence depicted by SEQ ID NO:2. Kipriyanov, et al. (1997) merely discloses a 274 amino acid sequence of a "scFv derived from hybridoma OKT3" (page 448, Figure 2B). SEQ ID NO:2 depicts a 291 amino acid sequence. Since **Kipriyanov, et al. (1997) does not teach the amino acid sequence of SEQ ID NO:2**, Kipriyanov, et al. (1997) must not anticipate the claims containing this element.

For the reason stated above, the 35 U.S.C. § 102(a) rejection of Claims 1-9, 12-25 and 27 over Kipriyanov, et al. (1997) should be withdrawn.

7. 35 U.S.C. § 103(a)

The Examiner rejects Claims 1-2, 4-9 and 12-22 under 35 U.S.C. § 103(a) as being obvious over Kroon, et al. (*Pharmaceutical Res.* 9:1386-93, 1992) in view of Kipriyanov, et al (*J. Immunol. Meth.* 196:51-62, 1996) and in further view of Senoo, et al. (U.S. Patent No. 5,852,177). Applicants respectively traverse the rejection of Claims 1-2, 4-9 and 12-22.

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

None of the cited references, Kroon, et al., Kipriyanov, et al. (1996) and Senoo, et al., alone or in combination, teach or suggest the amino acid sequence of SEQ ID NO:2. Since the cited references do not teach or suggest the amino acid sequence of SEQ ID NO:2, therefore the alleged prior art references do not establish prima facie obviousness of Claims 1-2, 4-9 and 12-22.

For the reasons stated above, the 35 U.S.C. § 103(a) rejection of Claims 1-2, 4-9 and 12-22 over Kroon, et al. in view of Kipriyanov, et al (1996) and in further view of Senoo, et al. should be withdrawn.

The Examiner rejects Claim 26 under 35 U.S.C. § 103(a) as being obvious over Kipriyanov, et al (1997) and Nitta, et al. (*The Lancet*, 335:368-71, 1990). Applicants respectively traverse this rejection of Claim 26.

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

For the reasons provided earlier, Kipriyanov, et al. (1997) is not a prior art reference. In addition, Nitta, et al. do not teach or suggest the amino acid sequence of SEQ ID NO:2. Therefore the alleged prior art references do not establish prima facie obviousness of Claim 26.

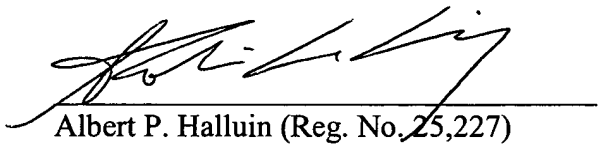
For the reasons stated above, the 35 U.S.C. § 103(a) rejection of Claim 26 over Kipriyanov, et al. (1997) and Nitta, et al. should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, the Applicants believe the application is in good and proper condition for allowance. Early notification of allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 463-8109. A telephone conference is especially requested if the Examiner intends to maintain the present rejections.

Respectfully submitted,

Date: September 18, 2001



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MARKED-UP VERSION OF THE REPLACEMENT PARAGRAPHS AND CLAIMS

In the Specification

On page 1, under the first paragraph cross-referencing the related applications, please insert the following heading:

--FIELD OF INVENTION--

On page 1, under the top paragraph, insert the following heading:

--BACKGROUND OF THE INVENTION--

On page 2, under the top paragraph, following the line "and its use.", insert the following heading:

--SUMMARY OF THE INVENTION--

On page 2, in the paragraph beginning on line 15, amend as follows:

For the production of an antibody according to the invention, mRNA from freshly subcloned hybridoma cells of OKT3 is used as a basis. The cDNA is produced according to methods known to a person skilled in the art, which were described in Dübel et al., J. Immunol. Methods 175, pp. 89-95 91994), for example. The DNA coding for the variable domain of the light chain can be produced by means of PCR using suitable primers, e.g. by means of primers Bi5 (5'-GGGAAGATGGATCCAGTTGGTGCAGCATCAGC (SEQ ID NO:8)) and Bi8 (5'-GGTGATATCGTKCTCACYCARTCTCCAGCAAT (SEQ ID NO:9)) which hybridize to the amino-terminal part of the constant domain of the κ-chain and the framework1 (FR1) region of the variable domain of the κ-chain (Dübel et al., see above). For the amplification of the DNA which codes for the variable domain of the heavy chain, it is possible to use e.g. the primer Bi4 (5'-CCAGGGGCCAGTGGATAGACAAGCTTGGGTGTCGTTTT (SEQ ID NO:10)) which hybridizes to the amino-terminal part of the constant domain 1 of the γ-chain (Dübel et al., cf.

above) and the primer Bi3f (5'-CAGCCGGCCATGGCGCAGGTSCAGCTGCAGSAGTCWGG (SEQ ID NO:11)) which hybridizes to the FR1 region of the heavy chain (Gotter et al., Tumor Targeting 1, pp. 107-114 (1995).

On page 4, under the fourth paragraph, following the line "figures.", insert the following heading:

--DESCRIPTION OF THE FIGURES--

On page 5, the paragraph beginning on line 17, amend as follows:

Figures 3A and 3B: bispecific antibody composed of mutated OKT3 and anti-CD19.

On page 5, under the third paragraph, following the line "anti-CD19", insert the following heading:

--DETAILED DESCRIPTION OF THE INVENTION--

In the Claims

1. (Twice Amended) A recombinant antibody product, comprising the V_H domain of the [OKT3] antibody produced by the hybridoma of ATCC deposit number CRL 8001 , wherein the cysteine at position H100A of said V_H domain is substituted with a polar amino acid , wherein said position H100A is according to the Kabat numbering system , wherein said recombinant antibody product comprises the amino acid sequence depicted by SEQ ID NO:2 .

2. (Twice Amended) The recombinant antibody product according to claim 1 , characterized in that the polar amino acid is serine.

Please cancel Claim 3.

4. (Twice Amended) A method for the production of the recombinant antibody product according to [any one of] claim[s] 1 [to 3] or 2 , characterized by the steps of:

a) obtaining mRNA from freshly subcloned hybridoma cells of [OKT3] ATCC deposit number CRL 8001 and transcription into cDNA,

b) amplifying the DNA coding for the variable domains of the light and heavy chains by means of PCR,

c) cloning of the DNA obtained in b) into a vector adapted for site-specific mutagenesis as well as introduction of a mutation in said position H100A of the V_H domain, wherein said position H100A is according to the Kabat numbering system, wherein said mutation is the substitution of a cysteine with a polar amino acid, and

d) inserting the mutated DNA obtained in c) in an expression vector and expression in a suitable expression system.

5. (Amended) The method according to claim 4, wherein the [primers used in] amplifying of step b) [are Bi5, Bi8, Bi4 and Bi3f] uses primers having the nucleotide sequences depicted by SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10 and SEQ ID NO:11 .

6. (Amended) The method according to claim 4, wherein the vector used in step c) is pCR-Skript SK(+).

7. (Amended) The method according to claim 4, wherein said cloning uses a primer comprising the sequence depicted by SEQ ID NO: 7.

Please cancel Claim 8.

9. (Amended) The method according to claim 4, wherein the expression takes place in XLl-Blue E. *coli* cells.

12. (Reiterated) The method according to claim 5, wherein the vector used in step c) is pCR-Skript SK(+).

13. (Reiterated) The method according to claim 5, wherein said cloning uses a primer comprising the sequence depicted by SEQ ID NO: 7.

14. (Reiterated) The method according to claim 6, wherein said cloning uses a primer comprising the sequence depicted by SEQ ID NO: 7.

Please cancel Claims 15-17.

18. (Reiterated) The method according to claim 4, wherein the expression takes place in XLl-Blue E. *coli* cells.

19. (Reiterated) The method according to claim 5, wherein the expression takes place in XLl-Blue E. *coli* cells.

20. (Reiterated) The method according to claim 6, wherein the expression takes place in XLl-Blue E. *coli* cells.

21. (Reiterated) The method according to claim 7, wherein the expression takes place in XLl-Blue E. *coli* cells.

Please cancel Claim 22.

23. (Reiterated) A peptide comprising the amino acid sequence depicted by SEQ ID NO:2.

24. (Reiterated) An antibody comprising the peptide according to Claim 23.

25. (Reiterated) A single-chain antibody comprising the peptide according to Claim 23.

26. (Reiterated) A bispecific antibody comprising the peptide according to Claim 23.

27. (Reiterated) A recombinant antibody product comprising the peptide according to Claim 23.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

On page 1, the following heading is under the first paragraph cross-referencing the related applications:

FIELD OF INVENTION

On page 1, the following heading is under the top paragraph:

BACKGROUND OF THE INVENTION

On page 2, the following heading is under the top paragraph, following the line "and its use.":

SUMMARY OF THE INVENTION

On page 2, the paragraph beginning on line 15 should read:

For the production of an antibody according to the invention, mRNA from freshly subcloned hybridoma cells of OKT3 is used as a basis. The cDNA is produced according to methods known to a person skilled in the art, which were described in Dübel et al., J. Immunol. Methods 175, pp. 89-95 91994), for example. The DNA coding for the variable domain of the light chain can be produced by means of PCR using suitable primers, e.g. by means of primers Bi5 (5'-GGGAAGATGGATCCAGTTGGTGCAGCATCAGC (SEQ ID NO:8)) and Bi8 (5'-GGTGATATCGTKCTCACYCARTCTCCAGCAAT (SEQ ID NO:9)) which hybridize to the amino-terminal part of the constant domain of the κ-chain and the framework1 (FR1) region of the variable domain of the κ-chain (Dübel et al., see above). For the amplification of the DNA which codes for the variable domain of the heavy chain, it is possible to use e.g. the primer Bi4 (5'-CCAGGGGCCAGTGGATAGACAAGCTTGGGTGTCGTTTT (SEQ ID NO:10)) which hybridizes to the amino-terminal part of the constant domain 1 of the γ-chain (Dübel et al., cf.

above) and the primer Bi3f (5'-CAGCCGGCCATGGCGCAGGTSCAGCTGCAGSAGTCWGG (SEQ ID NO:11)) which hybridizes to the FR1 region of the heavy chain (Gotter et al., Tumor Targeting 1, pp. 107-114 (1995).

On page 4, the following heading is under the fourth paragraph, following the line "figures.":

DESCRIPTION OF THE FIGURES

On page 5, the paragraph beginning on line 17 should read:

Figures 3A and 3B: bispecific antibody composed of mutated OKT3 and anti-CD19.

On page 5, the following heading is under the third paragraph, following the line "anti-CD19":

DETAILED DESCRIPTION OF THE INVENTION

In the Claims

1. (Twice Amended) A recombinant antibody product, comprising the V_H domain of the antibody produced by the hybridoma of ATCC deposit number CRL 8001, wherein the cysteine at position H100A of said V_H domain is substituted with a polar amino acid, wherein said position H100A is according to the Kabat numbering system , wherein said recombinant antibody product comprises the amino acid sequence depicted by SEQ ID NO:2.

2. (Twice Amended) The recombinant antibody product according to claim 1, characterized in that the polar amino acid is serine.

Claim 3 is cancelled.

4. (Twice Amended) A method for the production of the recombinant antibody product according to claim 1 or 2, characterized by the steps of:

a) obtaining mRNA from freshly subcloned hybridoma cells of ATCC deposit number CRL 8001 and transcription into cDNA,

b) amplifying the DNA coding for the variable domains of the light and heavy chains by means of PCR,

c) cloning of the DNA obtained in b) into a vector adapted for site-specific mutagenesis as well as introduction of a mutation in said position H100A of the V_H domain, wherein said position H100A is according to the Kabat numbering system, wherein said mutation is the substitution of a cysteine with a polar amino acid, and

d) inserting the mutated DNA obtained in c) in an expression vector and expression in a suitable expression system.

5. (Amended) The method according to claim 4, wherein the amplifying of step b) uses primers having the nucleotide sequences depicted by SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10 and SEQ ID NO:11 .

6. (Amended) The method according to claim 4, wherein the vector used in step c) is pCR-Skript SK(+).

7. (Amended) The method according to claim 4, wherein said cloning uses a primer comprising the sequence depicted by SEQ ID NO: 7.

Claim 8 is cancelled.

9. (Amended) The method according to claim 4, wherein the expression takes place in XLl-Blue E. *coli* cells.

12. (Reiterated) The method according to claim 5, wherein the vector used in step c) is pCR-Skript SK(+).

13. (Reiterated) The method according to claim 5, wherein said cloning uses a primer comprising the sequence depicted by SEQ ID NO: 7.

14. (Reiterated) The method according to claim 6, wherein said cloning uses a primer comprising the sequence depicted by SEQ ID NO: 7.

Claims 15-17 are cancelled.

18. (Reiterated) The method according to claim 4, wherein the expression takes place in XLl-Blue E. *coli* cells.

19. (Reiterated) The method according to claim 5, wherein the expression takes place in XLl-Blue E. *coli* cells.

20. (Reiterated) The method according to claim 6, wherein the expression takes place in XLl-Blue E. *coli* cells.

21. (Reiterated) The method according to claim 7, wherein the expression takes place in XLl-Blue E. *coli* cells.

Claim 22 is cancelled.

23. (Reiterated) A peptide comprising the amino acid sequence depicted by SEQ ID NO:2.

24. (Reiterated) An antibody comprising the peptide according to Claim 23.

25. (Reiterated) A single-chain antibody comprising the peptide according to Claim 23.

26. (Reiterated) A bispecific antibody comprising the peptide according to Claim 23.

27. (Reiterated) A recombinant antibody product comprising the peptide according to Claim 23.